21 May 2026
EMADOC-1700519818-3293183
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Xofluza

Baloxavir marboxil

Procedure no: EMA/PAM/0000328208

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	CHMP Rapporteur AR	28 April 2026	28 April 2026
☐	CHMP comments	11 May 2026	11 May 2026
☐	Updated CHMP Rapporteur AR	13 May 2026	n/a
☒	CHMP outcome	21 May 2026	21 May 2026

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1. Introduction

On 9 February 2026, the MAH submitted a completed paediatric study for Xofluza, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study YV44465 (Dragonstone) is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

The granules for oral suspension represent the authorised formulation for the age subset. Palatability was assessed as a secondary objective.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for study YV44465 (Dragonstone)

2.3.2. Clinical study

Study YV44465 (Dragonstone)

Description

Study YV44465 (Dragonstone) was a multicenter, randomised, open-label, active-controlled (i.e., oseltamivir) study to assess the safety, pharmacokinetics (PK), and efficacy of baloxavir marboxil compared with oseltamivir in Chinese paediatric participants aged 1 to < 12 years with influenza symptoms within 48 hours of symptom onset.

Approximately 100 paediatric participants were planned to be enrolled. Of the overall sample size, approximately 1/3 participants who are 1 to < 5 years old and 2/3 participants who are 5 to < 12 years old were planned to be enrolled. Participants were screened and randomised on Day 1 and assigned in a 2:1 ratio to receive a single oral dose of baloxavir marboxil based on body weight (2 mg/kg for participants weighing <20 kg or 40 mg for participants weighing ≥ 20 kg to < 80 kg or 80 mg for those weighing ≥ 80 kg) granules for oral suspension or oseltamivir (BID dose based on body weight) for 5 days.

Re-screening of participants who failed to meet the inclusion and exclusion criteria was not permitted for the same illness episode, as the time from symptom onset to the treatment window was limited to 48 hours. Either drug was started at the time of randomisation.

The total study duration for each participant was 29 days, consisting of a 5-day treatment period (mandatory visits on Days 1, 2, and 4) and a 24-day follow-up period (mandatory visits on Days 6, 10, and 29). The following assessments were conducted during clinic visits: physical examinations, vital signs, adverse events (AEs), concomitant therapies, clinical laboratory tests, and nasal/throat swabs. Visits on

Day 29 or early termination visits were conducted remotely. Throughout the treatment follow-up periods, the parents/caregivers maintained a participant diary for each participant in order to record body temperatures (tympanic assessment), influenza symptoms, and acetaminophen use.

Temperatures were recorded as follows:

• Days 1−3: 4 times daily (morning, noon, evening, and bedtime);

• Days 4−9: BID (morning and evening);

• Days 10−15: once daily.

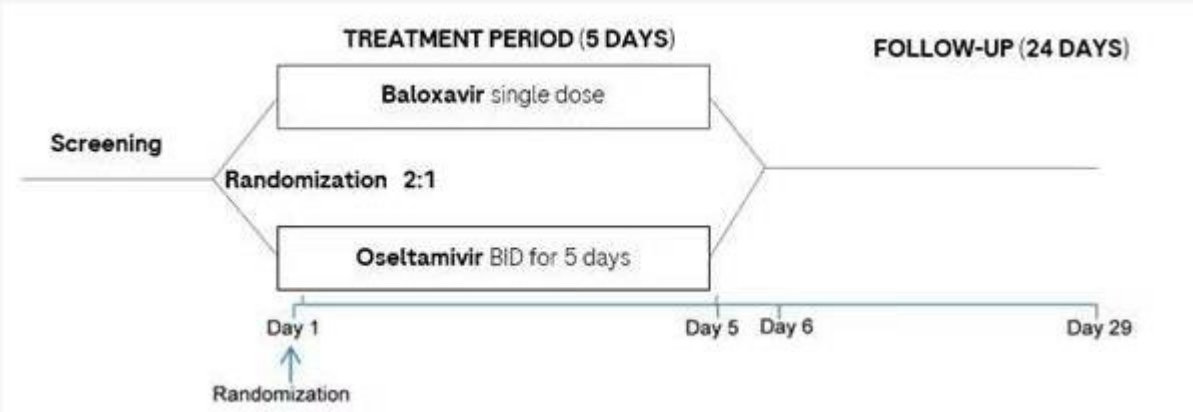
Influenza symptoms were recorded as follows:

• Days 1−9: twice a day (morning and evening)

• Days 10−15: once a day.

The study design is depicted in Figure 1:

Figure 1 – Study design



Methods

Study participants

Study YV44465 enrolled Chinese paediatric participants aged 1 to <12 years with influenza symptoms.

Inclusion Criteria

Potential participants were eligible to be included in the study only if all of the following key criteria applied:

• Age 1 to <12 years at the time of signing ICF

• A participant who had a diagnosis of influenza virus infection and met all the following conditions.

– Fever ≥38°C (tympanic temperature) at screening

AND

– At least one of the respiratory symptoms of influenza virus infection (e.g., cough and nasal discharge/nasal congestion)

AND

– A rapid influenza diagnostic test or polymerase chain reaction (PCR) showed positive for influenza A/B, e.g., point-of-care/local laboratory results with use of nasal aspirate, throat swab, or nasal drip/droplet (or other appropriate sample)

Results from local testing as part of standard of care were acceptable if samples were collected within 24 hours of screening and recorded in the participants' medical records.

• The time interval between the onset of symptoms and screening was≤ 48 hours (the onset of symptoms was defined as the time when body temperature first exceeded 37.5°C if known, or the time when the first symptom was noticed by participant, parent, or caregiver)

• PCR (-) or antigen test (-) for severe acute respiratory virus-coronavirus 2 (SARS-CoV-2) using point-of-care/local laboratory test with nasal aspirate, throat swab, or nasal drip/droplet (or other appropriate sample)

Results from local testing as part of standard of care were acceptable if samples were collected within 24 hours of screening and recorded in the participants' medical records.

Exclusion Criteria

Potential participants were excluded from the study if any of the following key criteria applied:

- A participant having severe influenza virus infection symptoms requiring inpatient treatment
- Evidence of severe renal impairment (equivalent to creatinine clearance<30 mL/min or estimated glomerular filtration rate<30 mL/min/1.73 m2), vascular, neurologic, or metabolic disease (e.g., diabetes, thyroid disorders, adrenal disease), uncontrolled hepatitis, cirrhosis, or pulmonary disease (e.g. uncontrolled bronchial asthma)
- Received systemic corticosteroid or immunosuppressive therapy
- Primary immunodeficiency syndrome
- History of organ transplantation
- Human Immunodeficiency Virus infection
- Immunisation with a live/attenuated influenza vaccine in 2 weeks prior to randomisation
- Previous malignancy within the last 5 years or has an active cancer at any site
- Previous encephalitis/encephalopathy, uncontrolled epilepsy with antiepileptic drugs, or influenza virus infection-associated abnormal behaviour within the last 2 years
- Complications by an infection requiring systemic antibiotic drug, antifungal and/or antiviral drug at screening

- A participant who received any medications with anti-flu effect such as baloxavir, peramivir, oseltamivir, zanamivir, favipiravir, arbidol, amantadine or traditional Chinese anti-influenza medicines within 30 days before screening
- Known allergy and/or clinically problematic intolerance to baloxavir, oseltamivir and/or acetaminophen
- Diagnosed with or suspected SARS-CoV-2 infection, or close contacts of diagnosed or suspected SARS-CoV-2 infected participants
- A participant who received an investigational or unapproved drug product within 30 days or 5× the half-life before screening, whichever was longer

Treatments

The investigational medicinal product (IMP) for this study was baloxavir marboxil.

Oseltamivir (also an IMP) was administered as an active control.

Table 1 – Study treatment Description

	Baloxavir marboxil	**Oseltamivir**
Use	Experimental	Active comparator
Drug form	Granules for oral suspension	Capsules/oral suspension
Unit dose strength(s)	2 mg/mL	75 mg/capsule
Dosage level(s)	2 mg/kg, 40 mg or 80 mg single dose	30 mg, 45 mg, 60 mg, 75 mg BID
Formulation(s)	Refer to Pharmacy Manual	Refer to Pharmacy Manual
Packaging	50-mL glass bottle	Blister packs containing 10 capsules, 1 pack per box
Labeling	Per local requirements	Per local requirements
Route of administration	Oral suspension	Oral/oral suspension
Source	Sponsor	Sponsor

Dosing Regimen

Baloxavir marboxil was administered orally as a single dose on Day 1, only.

The granules for oral suspension were reconstituted with water to provide a fixed dose based on the body weight of the child (2 mg/kg for participants weighing< 20 kg, or 40 mg for participants weighing ≥ 20 kg to < 80 kg, and 80 mg for those weighing≥ 80 kg) (see Table 2).

Table 2 – Baloxavir Marboxil Administration by Treatment Group

Participant's Body Weight at Screening	Dose, Formulation
<20 kg	2 mg/kg, oral suspension
≥20 kg to <80 kg	40 mg (20 mL), oral suspension
≥80 kg	80 mg (40 mL), oral suspension

Participants took the oseltamivir capsule orally. If participants could not take the capsule, they took the oral suspension prepared by the capsule. The powder for suspension was reconstituted with water, to provide a fixed dose based on the body weight of the child. The first dose of oseltamivir was administered on Day 1 at the site by the investigator/study nurse and the investigator/study nurse gave training on the oseltamivir administration to the parents/guardians. Participants took the second dose of oseltamivir on Day 1 and Day 2 to Day 5 at home.

Oseltamivir was given orally 12 hours apart. If the first dose was taken after 4 p.m. (16:00 hours) on Day 1, the next dose was taken in the morning of Day 2. For these participants, the tenth dose was taken on the morning of Day 6. If the first dose was taken prior to 4 p.m. (16:00 hours) on Day 1, the next dose was taken in the evening of the same day (i.e., prior to midnight on the same calendar day with a minimum of 7 hours between doses). For these participants, the tenth dose was taken in the evening of Day 5 (Table 3).

Table 3 – Oseltamivir Administration by Treatment Group

Participant's Body Weight at Screening	Dose. Formulation
≤15 kg	30 mg BID, oral suspension
>15 kg to≤23 kg	45 mg BID, oral suspension
>23 kg to≤40 kg	60 mg BID, oral suspension
>40 kg	75 mg BID, oral/oral suspension

Objectives

The primary and secondary objectives for the study are presented in Table 4 while the remaining objectives and corresponding endpoints are presented in Table 5.

Table 4 – Primary and Secondary Objectives and Corresponding Estimand

Objective	Estimand
Safety (Primary) Objective	**Estimand Definition**
To describe the safety of a single dose of baloxavir marboxil compared with 5 days of oseltamivir administered BID in Chinese pediatric participants	• Population: All participants aged 1 to < 12 years with influenza symptoms who received at least 1 dose of study treatment • Endpoint: – Incidence, severity, and timing of adverse events, serious adverse events, with severity determined according to NCI CTCAE v5 – Change from baseline in vital sign measurements – Change from baseline in clinical laboratory test results • Treatment: – Experiment arm: baloxavir marboxil single dose – Control arm: oseltamivir 5 days BID • Intercurrent events and handling strategies: – Treatment discontinuation: treatment policy strategy – Rescue medication: treatment policy strategy • Population-level summary: – No formal statistical testing were conducted. Analyses were descriptive. – Incidence of adverse events, serious adverse events by System Organ Class, by Preferred Term and by worst severity – Change from baseline summaries were presented overall and by treatment with use of descriptive statistics, including means, standard deviations, medians, and ranges for continuous variables
Efficacy (Secondary) Objective	**Estimand Definition**
To describe the clinical efficacy of baloxavir marboxil compared with oseltamivir in Chinese pediatric participants	• Population: All participants aged 1 to < 12 years with influenza symptoms who received at least 1 dose of study treatment who have had a laboratory confirmation of influenza infection (PCR result) from any swab sample collected at baseline or during the study • Endpoints: – Time to alleviation of influenza signs and symptoms, defined as the length of time taken from the start of treatment to the point at which all

Objective	Estimand
	of the following criteria are met and remain so for at least 21.5 hours: A score of 0 (no problem) or 1 (minor problem) for cough and nasal symptoms (Items 14 and 15 of the CARIFS). A "yes" response to the following question on the CARIFS: "Since the last assessment has the subject been able to return to day care/school (if applicable), or resume his or her normal daily activity in the same way as performed prior to developing the flu?" (if possible). Return to afebrile state (tympanic temperature ≤37.2°C). – Duration of fever (time to return to afebrile state [tympanic temperature ≤37.2°C] and remaining so for at least 21.5 hours) – Duration of symptoms (alleviation of all symptoms as defined by a score of 0 [no problem] or 1 [minor problem] and remaining so for at least 21.5 hours, for all 18 symptoms specified in the CARIFS questionnaire) – Time to return to normal health and activity based on the CARIFS questionnaire – Frequency of influenza-related complications (death, hospitalization, radiologically confirmed pneumonia, bronchitis, sinusitis, otitis media, encephalitis/encephalopathy, febrile seizures, myositis) – Proportion of participants requiring antibiotics for influenza related complications • Treatment: – Experiment arm: baloxavir marboxil single dose – Control arm: oseltamivir 5 days BID • Intercurrent events and handling strategies: – Treatment discontinuation: treatment policy strategy – Rescue medication: treatment policy strategy • Population-level summary: No formal statistical testing were conducted. Analyses were descriptive. Time to event endpoints and duration endpoints were summarized with use of Kaplan Meier plots and median survival time for each treatment arm.
Virology (Secondary) Objective	**Estimand Definition**
• To evaluate the virological activity of baloxavir marboxil compared with	• Population: All participants aged 1 to <12 years with influenza symptoms who received at least 1 dose of study treatment who have had a laboratory

Objective	Estimand
oseltamivir in Chinese pediatric participants	confirmation of influenza infection (PCR result) from any swab sample collected at baseline or during the study • Endpoints: – Time to cessation of viral shedding by virus titer and by RT-PCR with use of samples from respiratory swabs – Change from baseline in influenza virus titer and in the amount of virus RNA (RT-PCR) at each timepoint with use of samples from respiratory swabs – Proportion of participants with positive influenza virus titer and proportion of participants positive by RT-PCR at each timepoint with use of samples from respiratory swabs – Area under the curve in virus titer and in the amount of virus RNA (RT-PCR) with use of samples from respiratory swabs • Treatment: – Experiment arm: baloxavir marboxil single dose – Control arm: oseltamivir 5 days BID • Intercurrent events and handling strategies – Treatment discontinuation: treatment policy strategy – Rescue medication: treatment policy strategy • Population-level summary: – Summaries were presented overall and by treatment with use of descriptive statistics, including means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables – Time to event endpoints were summarized with use of Kaplan Meier plots and median survival time.

BID = twice a day; CARIFS = Canadian Acute Respiratory Illness and Flu Scale;
NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events;
PCR = polymerase chain reaction; RT-PCR = reverse transcriptase polymerase chain reaction.

Table 5 – Other Secondary Objectives and Endpoints

Pharmacokinetic (Secondary) Objective	Corresponding Endpoints
• To describe the PK of baloxavir after single-dose administration of baloxavir marboxil in Chinese pediatric participants	• Plasma concentrations of S-033447 (active metabolite) will be summarized by time (C_{24} and C_{72}) and body weight • Population PK model derived parameters (e.g., AUC_{inf}, C_{max}, and other PK parameters as appropriate) (modeling report)
Virology (Secondary) Objective	**Corresponding Endpoints**
• To evaluate the polymorphic and treatment-emergent amino acid substitutions in the *PA* gene and drug susceptibility in participants with evaluable virus in Chinese pediatric participants	• Polymorphic and treatment-emergent amino acid substitutions in the *PA* gene • Drug susceptibility in participants with evaluable virus
Palatability (Secondary) Objective	**Corresponding Endpoint**
• To evaluate the palatability of the oral suspension	• Proportion of participants reporting each palatability and acceptability response (see Protocol Appendix 6)

AUC_{inf}=area under the concentration-time curve extrapolated to infinity; C_{24}=concentration at 24 hours postdose; C_{72}=concentration at 72 hours postdose; C_{max}=maximum observed concentration; PK=pharmacokinetic.

Outcomes/endpoints

Sample size

Approximately 100 paediatric participants were planned to be enrolled. Of the overall sample size, approximately 1/3 participants who were 1 to < 5 years old and 2/3 participants who were 5 to < 12 years old were planned to be enrolled.

Randomisation and blinding (masking)

Participants were randomised in a 2:1 ratio to a single oral dose of baloxavir marboxil based or oseltamivir. This was an open label study.

Statistical Methods

All the statistical analyses of efficacy endpoints were descriptive. The FASI population was used for all efficacy analyses.

Pharmacokinetic bioanalysis

The analysis of the plasma concentrations of baloxavir was conducted in accordance with a previously validated method. All samples were analysed within the proven stability and incurred sample reanalysis was within the acceptable range.

Safety of baloxavir marboxil was the primary objective of this study. No formal statistical testing or comparisons between baloxavir marboxil and oseltamivir were planned. All comparisons and analyses were descriptive.

Results

Participant flow

A total of 115 participants were screened for the study, of whom 15 participants failed screening criteria; mainly due to participants not meeting the criteria of diagnosis of influenza virus infection, based on information collected on the IxRS. A listing of all participants who failed screening, including the reasons for screen failure was provided.

Overall, 100 participants were randomised (67 participants in the baloxavir marboxil arm and 33 participants in the oseltamivir arm) in the study across 16 sites in China.

Of the 100 participants, 99 (99.0%) participants (66 [98.5%] participants in the baloxavir marboxil arm and 33 [100%] participants in the oseltamivir arm) entered follow-up period.

A total of 96 (96.0%) participants (64 [95.5%] participants in baloxavir marboxil arm and 32 [97.0%] participants in oseltamivir arm) completed the study.

The reason for study discontinuation in the participants were:

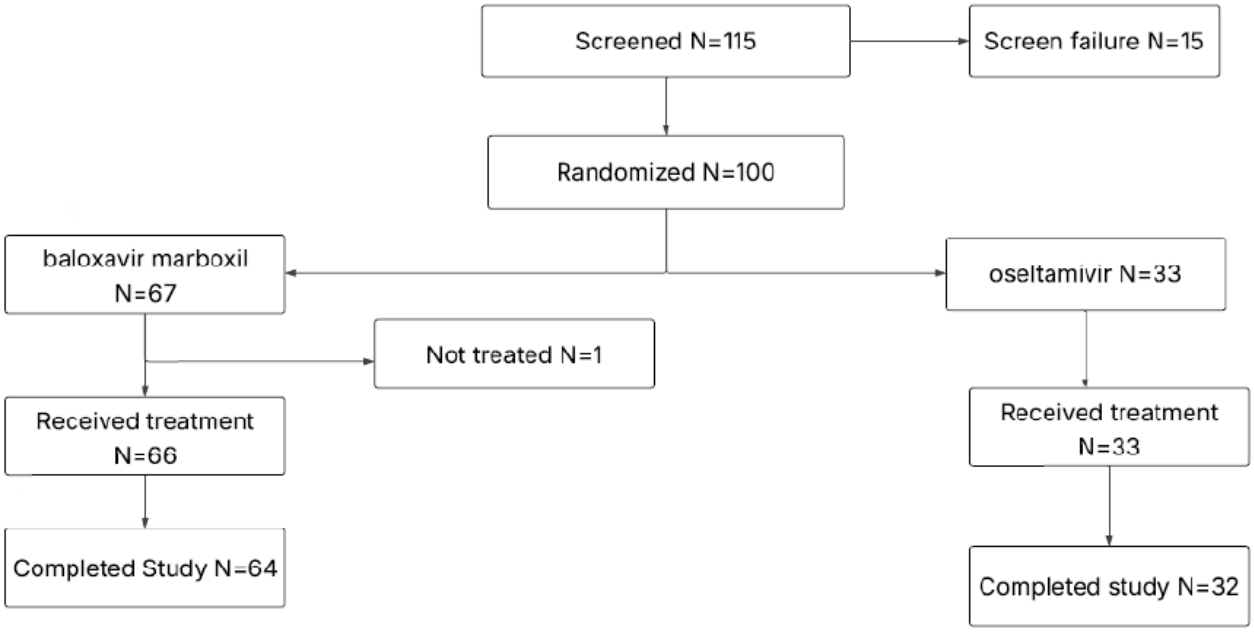
- Withdrawal by subject: 3 (4.5%) participants in the baloxavir marboxil arm
- Other: 1 (3.0%) participant in the oseltamivir arm

A total of 98 (98.0%) participants (66 [98.5%] participants in the baloxavir marboxil arm and 32 [97%] participants in the oseltamivir arm) completed the study treatment.

The reason for treatment discontinuation in the participants were:

- Withdrawal by subject: 1 (1.5%) participant in the baloxavir marboxil arm
- Physician decision: 1 (3.0%) participant in the oseltamivir arm

Figure 2 Participant Disposition



N = number of participants.

Recruitment

Baseline data

Demographic and baseline characteristics were largely similar between the treatment arms in the FAS population.

Of the 100 participants, 40 (40.0%) participants were enrolled from the age group of 1-<5 years while 60 (60.0%) participants were enrolled from the age group of 5-<12 years. The median age at baseline across both treatment arms was 5.0 years (range: 1-11 years).

Males and females were similarly represented in the study population; 55 (55.0%) participants were males while 45 (45.0%) participants were females.

Overall, 6 (6.0%) participants (4 [6.0%] participants in baloxavir marboxil arm and 2 [6.1%] participants in the oseltamivir arm) were vaccinated in past 12 months before screening and 5 (5.0%) participants (4 [6.0%] participants in baloxavir marboxil arm and 1 [3.0%] participant in the oseltamivir arm) had high-risk for influenza complications (Table 6).

Table 6 - Demographics and Baseline Characteristics, Full Analysis Set

	Baloxavir Marboxil (N=67)	Oseltamivir (N=33)	All Patients (N=100)
Age (years)			
n	67	33	100
Mean (SD)	5.1 (2.55)	5.3 (2.75)	5.2 (2.61)
Median	5.0	5.0	5.0
Min - Max	1 - 11	1 - 10	1 - 11
Age group (yr)			
n	67	33	100
1 - <5y	27 (40.3%)	13 (39.4%)	40 (40.0%)
5 - <12y	40 (59.7%)	20 (60.6%)	60 (60.0%)
Sex			
n	67	33	100
Female	34 (50.7%)	11 (33.3%)	45 (45.0%)
Male	33 (49.3%)	22 (66.7%)	55 (55.0%)
Ethnicity			
n	67	33	100
Not Hispanic or Latino	67 (100%)	33 (100%)	100 (100%)
Race			
n	67	33	100
Asian	67 (100%)	33 (100%)	100 (100%)
Weight (kg) at Baseline			
n	66	33	99
Mean (SD)	20.88 (8.71)	21.83 (9.48)	21.20 (8.94)
Median	19.15	19.00	19.00
Min - Max	9.1 - 57.0	10.0 - 51.5	9.1 - 57.0
Height (cm) at Baseline			
n	66	33	99
Mean (SD)	111.94 (17.69)	114.55 (18.18)	112.81 (17.80)
Median	111.30	112.00	111.50
Min - Max	79.6 - 150.0	75.0 - 148.0	75.0 - 150.0
BMI at Baseline			
n	66	33	99
Mean (SD)	16.06 (2.21)	16.04 (3.39)	16.05 (2.64)
Median	15.57	15.51	15.54
Min - Max	11.8 - 25.7	11.1 - 32.4	11.1 - 32.4
Vaccination Status			
n	67	33	100
Yes	4 (6.0%)	2 (6.1%)	6 (6.0%)
No	63 (94.0%)	31 (93.9%)	94 (94.0%)
Subtype by PCR			
n	61	31	92
B	2 (3.3%)	1 (3.2%)	3 (3.3%)
H1_2009	56 (91.8%)	28 (90.3%)	84 (91.3%)
H3	2 (3.3%)	1 (3.2%)	3 (3.3%)
UNKNOWN	1 (1.6%)	1 (3.2%)	2 (2.2%)
High Risk for influenza complications			
n	67	33	100
Yes	4 (6.0%)	1 (3.0%)	5 (5.0%)
No	63 (94.0%)	32 (97.0%)	95 (95.0%)

Overall for 92 (92.0%) participants with influenza subtype by RT-PCR at baseline or post-baseline, the predominant subtype was H1_2009 (84 [91.3%] participants) for both arms (56 [91.8%] in the baloxavir marboxil arm vs. 28 [90.3%] participants in the oseltamivir arm). Overall numbers were low for subtype H3 (2 [3.3%] participants in the baloxavir marboxil arm vs. 1 [3.2%] participant in the oseltamivir arm) and influenza B in both arms (2 [3.3%] in the baloxavir marboxil arm vs. 1 [3.2%] participant in the oseltamivir arm). The subtype could not be determined for 2 participants (1 [1.6%] participant in the baloxavir marboxil arm vs. 1 [3.2%] participant in the oseltamivir arm).

Among the 92 participants in the FASI population, demographic and baseline characteristics were comparable to those in the FAS population.

Medical History

Overall, 35 (52.2%) participants in the baloxavir marboxil arm and 17 (51.5%) participants in the oseltamivir arm reported at least one previous medical condition.

The most common previous medical condition by System organ class (SOC) reported in≥10% of participants in either arm (baloxavir marboxil arm vs. oseltamivir arm; respectively) were:

• Infections and infestations: 19 (28.4%) participants vs. 8 (24.2%) participants

• Respiratory, thoracic and mediastinal disorders: 15 (22.4%) participants vs. 5 (15.2%) participants

• Skin and subcutaneous tissue disorders: 1 (1.5%) participant vs. 4 (12.1%) participants

There were participants enrolled in this study with disorders which may otherwise be considered high risk complications for influenza according to Centers for Disease Control and Prevention (CDC, 2018) criteria, these included 4 of the participants with asthma/cough variant asthma and 1 of the participants with Thalassemia. However, all of these participants were considered to be stable with controlled disease at baseline and were therefore enrolled into the study as per the eligibility criteria.

Prior Procedures and Surgeries

Overall, 7 participants in the baloxavir marboxil arm and 2 participants in the oseltamivir arm reported at least one previous surgery or procedure.

Prior Medication

Overall, 29 (43.3%) participants in baloxavir marboxil arm and 24 (72.7%) participants in oseltamivir arm received at least one prior medication, started before the first dose of study treatment and ended before or after the first dose of study treatment.

The most frequently reported prior medications in ≥ 10% of participants receiving treatment across either of the arms (baloxavir marboxil arm vs. oseltamivir arm; respectively) were ibuprofen (14 [20.9%] participants vs. 12 [36.4%] participants) and paracetamol (5 [7.5%] participants vs 6 [18.2%] participants).

Concomitant Medication

Overall, 62 (92.5%) participants in baloxavir marboxil arm and 33 (100%) participants in oseltamivir arm received at least one concomitant medication started before the first dose of study treatment and ended after the first dose of study treatment.

The most frequently reported concomitant medications with≥ 10% participants receiving treatment across either of the arms (baloxavir marboxil arm vs. oseltamivir arm; respectively) were paracetamol (61 [91.0%] participants vs. 33 [100%] participants), ibuprofen2 (24 [35.8%] participants vs. 12 [36.4%] participants), ambroxol hydrochloride; clenbuterol hydrochloride (9 [13.4%] participants vs 6 [18.2%] participants), potassium chloride (8 [11.9%] participants vs. 1 [3.0%] participant) and sodium chloride (7 [10.4%] participants vs. 1 [3.0%] participant.

Number analysed

The full analysis set (FAS) comprised of 100 participants.

The primary objective for this study was safety; the safety analysis set comprised of 99 participants. One participant assigned to the baloxavir marboxil arm was not treated and was excluded from the safety analysis set.

The efficacy analysis was based on the full analysis set-infected (FASI) participants and comprised of 92 participants, this included all participants who received any amount of study treatment and who had a laboratory confirmation of influenza infection (reverse transcriptase polymerase chain reaction [RT-PCR] result) from any swab sample collected at baseline or during the study. Eight participants who were not confirmed positive by the PCR result from central laboratory were excluded from the FASI population.

The PK analysis set comprised of 44 participants.

Exposure to Study Treatment

A total of 66 participants (27 participants in 1–< 5 years age group and 39 participants in 5–<12 years age group) in the baloxavir marboxil arm and 33 participants (13 participants in 1–< 5 years age group and 20 participants in 5–< 12 years age group) in the oseltamivir arm received the study treatment.

All participants in the baloxavir marboxil received their single dose of baloxavir marboxil granules; 36 participants received body-weight adjusted dosing of 2 mg/kg and 30 participants received a flat dose of 40 mg. For oseltamivir arm, the median duration was 5 days (range: 3−6 days).

Exposure duration was consistent across both age groups for both study treatments.

Compliance with Treatment

The median compliance rate was 100% (range: 99−104) in the baloxavir marboxil arm and 100% (range: 70−100) in the oseltamivir arm.

Note: compliance for baloxavir marboxil was based on the expected amount of drug administered; compliance for oseltamivir was based on the expected frequency of drug administration. The slight variation in treatment compliance within baloxavir marboxil arm resulted from the rounding-off method applied during drug administration.

Compliance was consistently high with a median of 100% across both age groups (1- <5 years old and 5 - <12 years old). All participants in both the arms reported compliance rate≥ 80%, except for 1 participant in the oseltamivir arm in the 1-<5 years age group reported compliance rate<80%.

There were no participants with medication error or dosing error across both arms. One case of drug misuse was reported in the oseltamivir arm, where the participant continued taking oseltamivir after

being told by the investigator to discontinue treatment. No associated AEs were reported for this participant.

Efficacy results

Table 7 - Summary of Time-to-Event Secondary Efficacy Endpoints (FASI Population)

	Baloxavir marboxil arm (N=61)	Oseltamivir arm (N=31)
Time to alleviation of influenza signs and symptoms (TTAS)		
Participants included in the analysis [a]	60	31
Participants with event (%)	53 (88.3%)	30 (96.8%)
Median (95% CI) hours	**126.1** (92.2, 141.1)	**119.5** (90.5, 160.0)
Supplementary Analysis for Time to alleviation of influenza signs and symptoms [b]		
Participants included in the analysis [a]	58	30
Participants with event (%)	55 (94.8%)	29 (96.7%)
Median (95% CI) hours	**44.0** (39.4, 53.0)	**55.0** (42.2, 87.2)
Duration of fever (return to afebrile state)		
Participants with fever at baseline	57	27
Participants with event (%)	56 (98.2%)	26 (96.3%)
Median (95% CI) hours	**28.3** (23.3, 38.9)	**36.1** (29.3, 44.0)
Duration of symptoms		
Participants included in the analysis	61	31
Participants with event (%)	57 (93.4%)	30 (96.8%)
Median (95% CI) hours	**43.9** (35.0, 76.6)	**51.9** (34.5, 71.0)
Time to return to normal health and activity		
Participants included in the analysis [a]	54	29
Participants with event (%)	49 (90.7%)	28 (96.6%)
Median (95%CI] hours	**126.0** (81.8, 137.8)	**115.3** (88.4, 136.7)
Frequency of influenza-related complication		
Participants with event (%)	**2 (3.3%)**	0
Proportion requiring antibiotics		
Participants (%)	**1 (1.6%)**	0

CARIFS=Canadian Acute Respiratory Illness and Flu Scale; CI = confidence interval; FASI = full analysis set-infected; N = number of participants.

a Participant who fulfilled the endpoint definition at baseline was excluded from the analysis.

b The supplementary analysis was conducted in which the following criterion was removed from the calculation of the TTAS: A "yes" response to the following question on the CARIFS: "Since the last assessment has the subject been able to return to day care/school, or resume his or her normal daily activity in the same way as performed prior to developing the flu?"

Time to Alleviation of Influenza Signs and Symptoms

All participants were included in the analysis except one participant in baloxavir marboxil arm who was excluded from the analysis because the participant fulfilled the TTAS endpoint definition at baseline.

TTAS was comparable between the two treatment arms: median 126.1 hours (95% CI: 92.2, 141.1) in the baloxavir marboxil arm compared with median 119.5 hours (95% CI: 90.5, 160.0) in the oseltamivir arm (Table 8). Participants with no alleviation of signs and symptoms were censored at their last assessment.

The Kaplan-Meier curves of the TTAS shown in Figure 3 further highlight that the TTAS was similar in both the treatment arms.

Table 8 - Summary of Time to Alleviation of Influenza Signs and Symptoms, Full Analysis Set-Infected Participants

Protocol: YV44465

Time to Alleviation (TTA) of Influenza Signs and Symptoms (Hours)

	Baloxavir Marboxil (N=61)	Oseltamivir (N=31)
Patients Included in the Analysis	60	31
Patients with event (%)	53 (88.3%)	30 (96.8%)
Patients Censored (%)	7 (11.7%)	1 (3.2%)
Time to event (hours) (a)		
Median (b)	126.1	119.5
95% CI	(92.2, 141.1)	(90.5, 160.0)
Min - Max	12 - 344*	26* - 308

Patients with symptom scores =< 1 for a score of 0 (no problem) or 1 (minor problem) for cough and nasal symptoms, as well as tympanic temperature =< 37.2C and a "yes" response to the question "Since the last assessment has the subject been able to return to day care/ school, or resume his or her normal daily activity in the same way as performed prior to developing the flu?" at baseline are excluded from the analysis.

(a) Time from start of treatment to the point as which all of the following criteria are met and remain so for at least 21.5 hours:

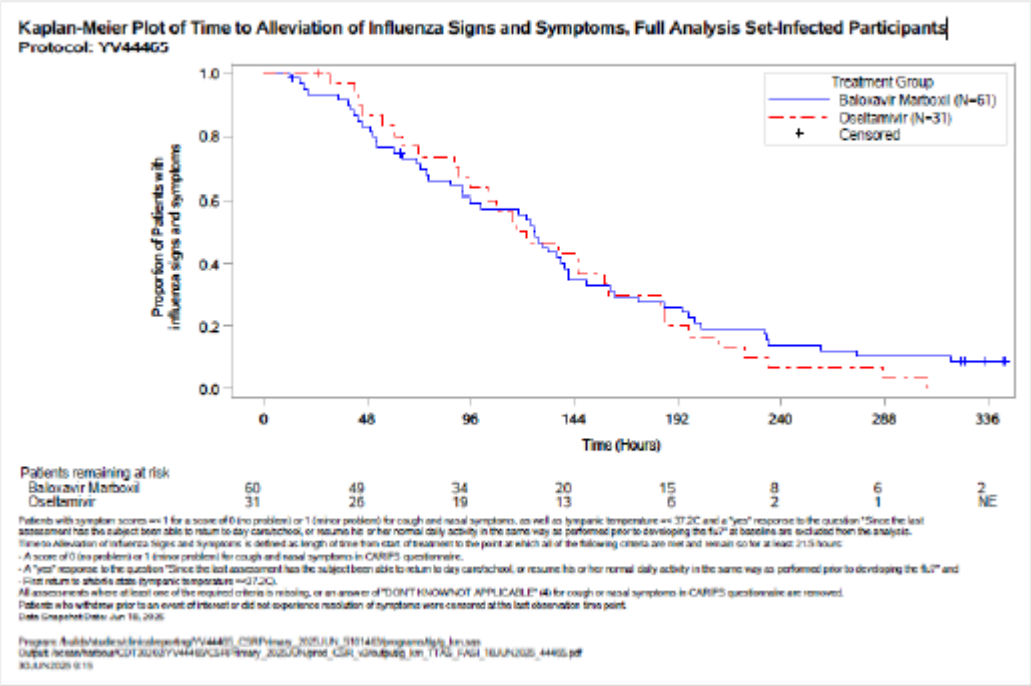
- A score of 0 (no problem) or 1 (minor problem) for cough and nasal symptoms in CARIFS questionnaire,
- A "yes" response to the question "Since the last assessment has the subject been able to return to day care/school, or resume his or her normal daily activity in the same way as performed prior to developing the flu?" and
- First return to afebrile state (tympanic temperature =<37.2°C).

All assessments where at least one of the required criteria is missing, or an answer of "DON'T KNOW/NOT APPLICABLE" (4) for cough or nasal symptoms in CARIFS questionnaire are removed.

(b) Median time was estimated from the Kaplan-Meier curve.

*: Censored time

Figure 3 Kaplan-Meier Plot of Time to Alleviation of Influenza Signs and Symptoms, Full Analysis Set-Infected Participants



Duration of fever

The median duration of fever was comparable between the treatment arms: baloxavir marboxil arm (28.3 hours [95% CI: 23.3, 38.9]) compared with the oseltamivir arm (36.1 hours [95% CI: 29.3, 44.0]).

Duration of Symptoms

The median duration of symptoms was comparable in the baloxavir marboxil arm (43.9 hours [95% CI: 35.0, 76.6]) and the oseltamivir arm (51.9 hours [95% CI: 34.5, 71.0]).

Time to Return to Normal Health and Activity

The median time to return to normal health and activity based on the CARIFS questionnaire was comparable between the treatment arms: baloxavir marboxil arm (126.0 hours [95% CI: 81.8, 137.8]) compared with the oseltamivir arm (115.3 hours [95% CI: 88.4, 136.7]). Participants who do not return to normal health and activity were censored at the last observation timepoint.

Frequency of Influenza-Related Complications

The overall incidence of influenza-related complications meeting pre-defined diagnostic criteria (death, hospitalisation, radiologically confirmed pneumonia, bronchitis, sinusitis, otitis media, encephalitis/encephalopathy, febrile seizures, myositis) was low and occurred only in the baloxavir marboxil arm: in 2 (3.3%) participants in that arm.

Pneumonia and bronchitis occurred in 1 (1.6%) participant each in the baloxavir marboxil arm. Both events resulted in hospitalisation of the participants so hospitalisation was reported in 2 (3.3%) participants in the baloxavir marboxil arm.

Virology

Time to Cessation of Viral Shedding by Virus Titer

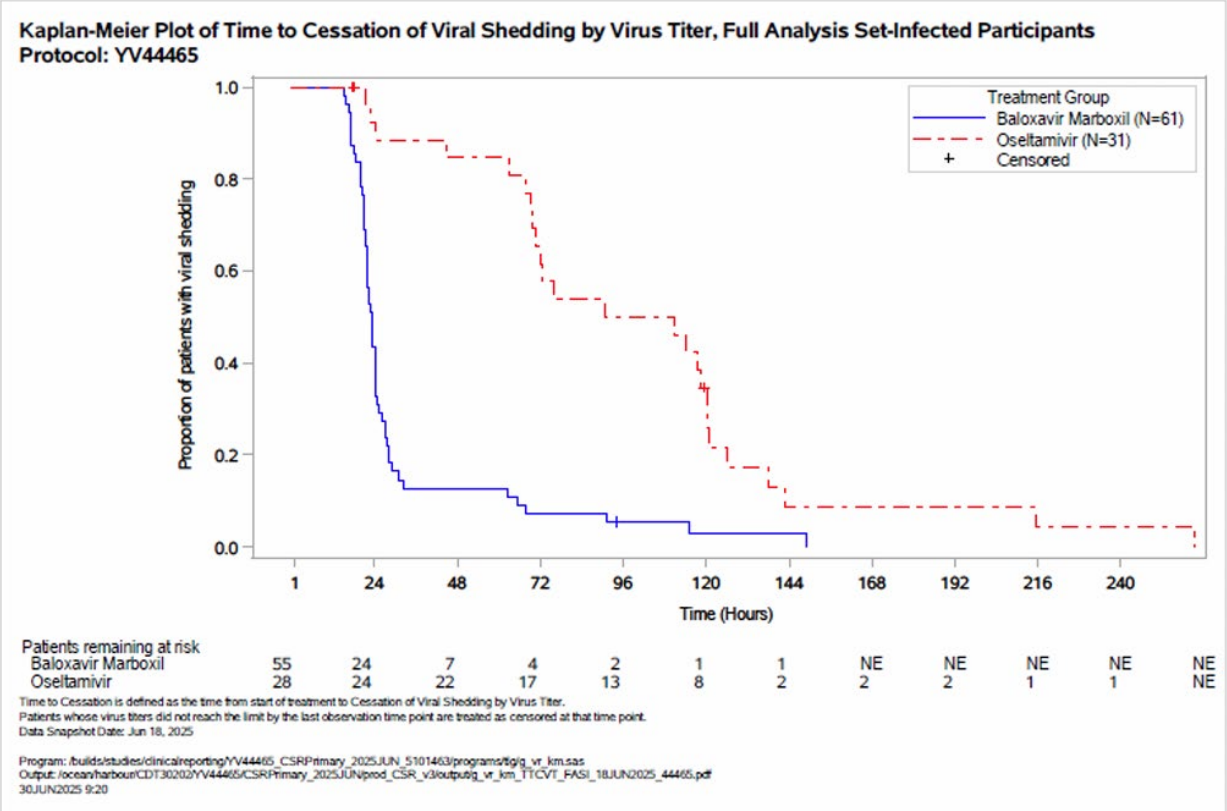
The time to cessation of viral shedding by virus titer endpoint is defined as the time, in hours, between the initiation of study treatment and first time when the influenza virus titer was below the lower limit of detection.

Among 55 participants in the baloxavir marboxil arm and 28 participants in the oseltamivir arm, with post-baseline virology assessment, the median time to cessation of viral shedding was shorter in the baloxavir marboxil arm (23.2 hours ([95% CI: 21.9, 24.4]) compared with the oseltamivir arm (100.7 hours [95% CI: 70.9, 120.3]).

Participants whose virus titers did not reach the limit by the last observation timepoint were treated as censored at that timepoint.

The Kaplan-Meier curves show a clear separation after 24 hours in favour of the baloxavir marboxil arm (Figure 4).

Figure 4 - Kaplan-Meier Plot of Time to Cessation of Viral Shedding by Virus Titer, Full Analysis Set-Infected Participants



Change from Baseline in Influenza Virus Titer at Each Timepoint

A greater decline in the mean change from baseline in influenza virus titer was observed in the baloxavir marboxil arm on Day 2 compared with the oseltamivir arm. The change from baseline reached a plateau by Day 2 for the baloxavir marboxil arm (median: -4.00; mean: -3.61 [SD 1.45] log10 TCID50/mL) compared with the oseltamivir arm on the same day (median: -3.00; mean: -3.11 log10 TCID50/mL [SD 1.34]). The change from baseline reached a plateau after Day 6 for the oseltamivir arm.

Proportion of Participants with Positive Influenza Virus Titer at Each Timepoint

The proportion of participants with positive influenza virus titer showed a large difference on Day 2 between the baloxavir marboxil arm (11.1%; 6/54 participants) compared with the oseltamivir arm (85.7%; 24/28 participants). At later timepoints the difference in proportions of participants with positive influenza virus titer became smaller in the baloxavir marboxil arm compared with the oseltamivir arm.

Area Under the Curve in Virus Titer

The area under the curve (AUC) in virus titer is presented by treatment arm and calculated using the trapezoidal method. The mean AUC values without adjustment for baseline were 177.40 log10 TCID50/mL·hours (SD 70.64) in the baloxavir marboxil arm and 308.67 log10 TCID50/mL·hours (SD 148.21) in the oseltamivir arm.

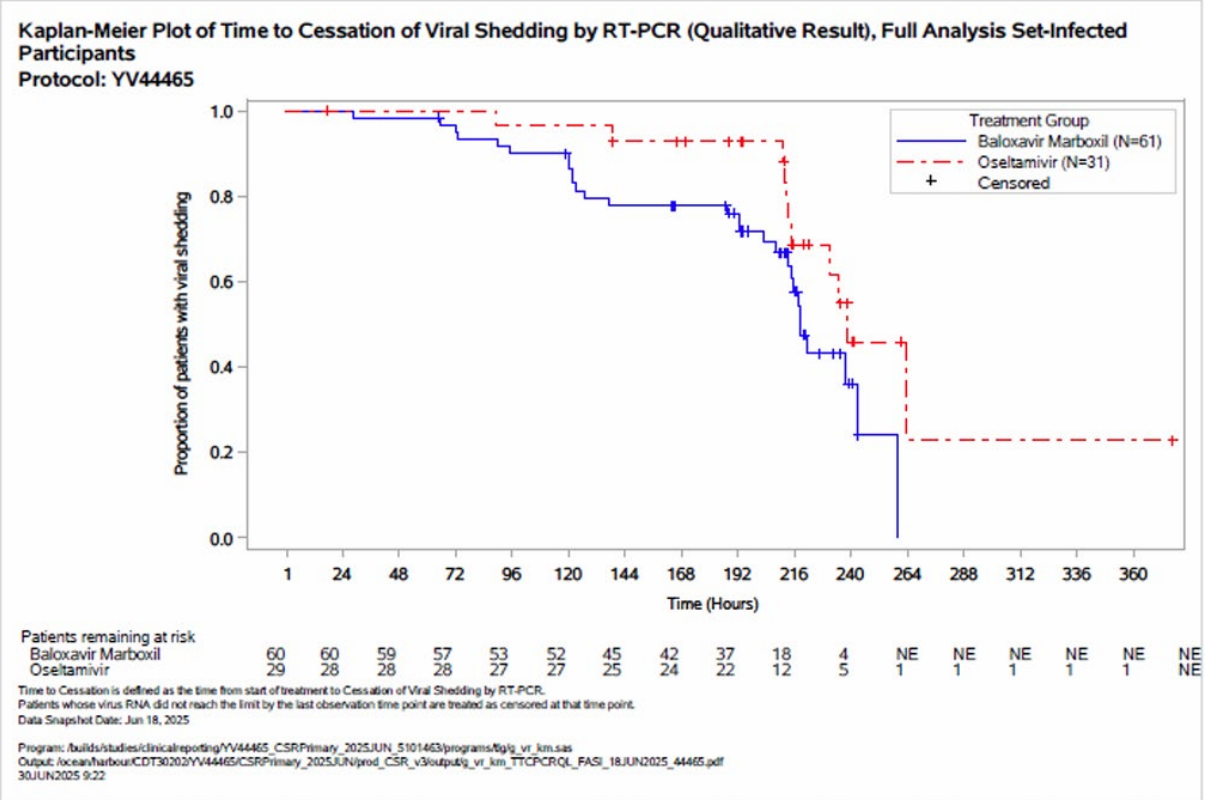
The mean AUC value with baseline adjustment was -536.09 log10 TCID50/mL·hours (SD 312.86) in the baloxavir marboxil arm and -610.11 log10 TCID50/mL·hours (SD 414.54) in the oseltamivir arm.

Time to Cessation of Viral Shedding by RT-PCR

Among 60 participants in the baloxavir marboxil arm and 29 participants in the oseltamivir arm, with post-baseline RT-PCR virology assessment, the median time to cessation of viral shedding was generally comparable between the baloxavir marboxil arm (218.4 hours ([95% CI: 214.8, 242.7]) and the oseltamivir arm (238.6 hours [95% CI: 214.8, NE]). Participants whose virus RNA had not reached the limit by the last observation timepoint were treated as censored at that timepoint.

The Kaplan-Meier curves show a generally similar trend for both arms (Figure 5).

Figure 5 - Kaplan-Meier Plot of Time to Cessation of Viral Shedding by RT-PCR (Qualitative Result), Full Analysis Set-Infected Participants



NE = not evaluable.

Change from Baseline in the Amount of Virus RNA (RT-PCR) at Each Timepoint

A greater decline in the mean change from baseline in the amount of virus RNA by RT-PCR was observed in the baloxavir marboxil arm up to Day 4 compared with the oseltamivir arm. The mean change from baseline on Day 4 was -2.79 log10 vp/mL [SD 1.39]) for the baloxavir marboxil arm compared with -1.82 log10 vp/mL [SD 1.71] in the oseltamivir arm. At later timepoints the differences from baseline in each arm were comparable.

Area Under the Curve in the Amount of Virus RNA (RT-PCR)

AUC unadjusted and adjusted for baseline was calculated using the trapezoidal method similar to AUC in virus titer. The mean AUC values without adjustment for baseline were 712.97 log10 vp/mL·hours (SD 308.74) in the baloxavir marboxil arm and 914.89 log10 vp/mL·hours (SD 366.58) in the oseltamivir arm. The mean AUC values with adjustment for baseline were -390.08 log10 vp/mL·hours (SD 263.39) in the baloxavir marboxil arm and -388.13 log10 vp/mL·hours (SD 325.99) in the oseltamivir arm.

Treatment-Emergent Amino Acid Substitutions in the PA Gene

In previous clinical studies, treatment-emergent PA/I38T substitution and additional I38 amino acid substitutions (PA/I38F, PA/I38M, PA/I38N, and PA/I38S), collectively referred to as PA/I38X, were observed, and reverse genetic analysis demonstrated that these substitutions were associated with reduced baloxavir marboxil susceptibility (Hashimoto et al. 2021). In addition, a PA/T20K substitution in

influenza B virus was also identified to be associated with reduced baloxavir susceptibility (Palmu et al. 2025). In the absence of published criteria for indicating reduced susceptibility to baloxavir marboxil, the current WHO guidelines for NAI (WHO 2025) were applied; thus, a >10-fold change in the baloxavir EC50 for the recombinant virus harbouring the amino acid substitution to that of the wild type strain was used to indicate reduced susceptibility to baloxavir marboxil for Type A virus and a >5-fold change was used to indicate reduced susceptibility for Type B virus.

None of the 59 participants with sequenced baseline samples for PA genotyping analysis had pre-existing I38X or T20K mutations. Of the 51 participants treated with baloxavir marboxil and with paired (pre and post dose) samples, 7 (13.7%) participants had treatment-emergent I38X or T20K substitutions. In influenza subtype A/H1_2009, 5 participants had treatment emergent amino acid substitution at position 38, 2 participants with I38T and 3 participants with I38T/I mixtures. Two participants infected with subtype A/H3N2 had I38X substitutions: 1 participant with I38T and 1 participant with a mixture of I38T/I. None of the participants with influenza B infection were found to have any amino acid substitutions in PA.

Drug Susceptibility in Participants with Evaluable Virus

Drug susceptibility was determined for virus from baseline samples in the baloxavir arm by measuring the half maximal effective concentration (EC50) for baloxavir. In the absence of established thresholds for baloxavir, reduced susceptibility was defined according to the WHO criteria for NAI as fold-changes in EC50 (EC50 / EC50 of reference) > 10 for influenza A and > 5 for influenza B viruses. As summarised in Table 9, all viruses at baseline showed EC50 fold-change values below those thresholds, indicating susceptibility to baloxavir of the tested viruses. Individual participant listings of drug susceptibility are provided.

Table 9 - Summary of Drug Susceptibility at Baseline, Full Analysis Set-Infected Participants

Baloxavir Marboxil (N=61)	Virus subtype based on PCR	Parameter	Statistics	
	B	BALOXAVIR EC50 for the sample (nmol/L)	n	2
			Mean (SD)	249.975 (17.8686)
			Median	249.975
			Min - Max	237.34 - 262.61
		EC50/EC50 for reference (a)	n	2
			Mean (SD)	4.224 (0.3019)
			Median	4.224
			Min - Max	4.01 - 4.44
	H1_2009	BALOXAVIR EC50 for the sample (nmol/L)	n	50
			Mean (SD)	48.454 (14.5612)
			Median	56.195
			Min - Max	11.14 - 60.64
		EC50/EC50 for reference (b)	n	50
			Mean (SD)	2.226 (0.6764)
			Median	2.397
			Min - Max	0.62 - 3.46
	H3	BALOXAVIR EC50 for the sample (nmol/L)	n	2
			Mean (SD)	35.950 (29.7692)
			Median	35.950
			Min - Max	14.90 - 57.00
		EC50/EC50 for reference (c)	n	2
			Mean (SD)	1.904 (1.5768)
			Median	1.904
			Min - Max	0.79

Palatability

A total 66 participants of baloxavir marboxil arm in the FAS population completed palatability assessment.

In response to the Question 1 of the palatability assessment (“How was the taste of the medicine?”), “Like very much”; “Like a little”; were each reported in 26 (39.4%) participants and 21 (31.8%) participants which illustrate majority of participants like the taste of the medicine. In response to the Question 2 of the palatability assessment (“Would you/the child be happy to take the medicine again?”), “Yes” was reported in majority; 43 (65.2%) of 66 participants.

Safety results

Frequency of Adverse Events by System Organ Class and Preferred Term

Overall, 24 (36.4%) participants in baloxavir marboxil arm and 12 (36.4%) participants in oseltamivir arm experienced a total of 46 AEs and 32 AEs; respectively during the study (Table 10).

The most frequently reported AEs by SOC (≥10% of participants) across either of the arms (baloxavir marboxil arm vs. oseltamivir arm) were:

• Gastrointestinal disorders: 11 (16.7%) participants vs. 9 (27.3%) participants

• Infections and infestations: 10 (15.2%) participants vs. 4 (12.1%) participants

• Investigations: 4 (6.1%) participants vs. 4 (12.1%) participants

Table 10 Safety Summary, Safety Analysis Set

Protocol: YV44465

	Baloxavir Marboxil (N=66)	Oseltamivir (N=33)	All Patients (N=99)
Total number of patients with at least one AE	24 (36.4%)	12 (36.4%)	36 (36.4%)
Total number of AEs	46	32	78
Total number of deaths	0	0	0
Total number of patients withdrawn from study due to an AE	0	0	0
Total number of patients with at least one			
AE with fatal outcome	0	0	0
Serious AE	2 (3.0%)	0	2 (2.0%)
Serious AE leading to withdrawal from treatment	0	0	0
Serious AE leading to any dose modification/interruption	0	0	0
Related Serious AE	0	0	0
AE leading to withdrawal from treatment	0	0	0
AE leading to dose modification/interruption	0	0	0
Related AE	2 (3.0%)	6 (18.2%)	8 (8.1%)
Related AE leading to withdrawal from any treatment	0	0	0
Related AE leading to dose modification/interruption	0	0	0
Severe AE (at greatest intensity)	4 (6.1%)	0	4 (4.0%)
AE of special interest	0	0	0

Investigator text for AEs encoded using MedDRA version 28.0.
Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Severe AE is defined as an AE with highest NCI CTCAE grade of 3 or above.

The most frequently reported AEs by PT (≥5% of participants) across either of the arms (baloxavir marboxil arm vs. oseltamivir arm) were (Table 11):

• Vomiting: 3 (4.5%) participants vs. 6 (18.2%) participants

• Functional gastrointestinal disorder: 2 (3.0%) participants vs. 2 (6.1%) participants

• Bronchitis: 5 (7.6%) participants vs. 0 participant

• Upper respiratory tract infection: 4 (6.1%) participants vs. 1 (3.0%) participant

• Rhinitis: 0 participant vs. 2 (6.1%) participants

Table 11 Summary of Adverse Events Occurring in ≥ 5% of Patients in at least One Treatment Group, Safety Analysis Set

Protocol: YV44465

MedDRA System Organ Class MedDRA Preferred Term	Baloxavir Marboxil (N=66)	Oseltamivir (N=33)	All Patients (N=99)
Total number of patients with at least one adverse event	14 (21.2%)	10 (30.3%)	24 (24.2%)
Overall total number of events	14	12	26
Gastrointestinal disorders			
Total number of patients with at least one adverse event	5 (7.6%)	8 (24.2%)	13 (13.1%)
Total number of events	5	8	13
Vomiting	3 (4.5%)	6 (18.2%)	9 (9.1%)
Functional gastrointestinal disorder	2 (3.0%)	2 (6.1%)	4 (4.0%)
Infections and infestations			
Total number of patients with at least one adverse event	9 (13.6%)	3 (9.1%)	12 (12.1%)
Total number of events	9	4	13
Bronchitis	5 (7.6%)	0	5 (5.1%)
Upper respiratory tract infection	4 (6.1%)	1 (3.0%)	5 (5.1%)
Rhinitis	0	2 (6.1%)	2 (2.0%)

Investigator text for AEs encoded using MedDRA version 28.0.
Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Adverse Events Related to Treatment

The proportion of participants with AEs assessed as treatment-related by the investigator was numerically lower in the baloxavir marboxil arm than in the oseltamivir arm (2/66 [3.0%] participants) vs. 18.2% [6/33 participants], respectively).

In the baloxavir marboxil arm, 2 participants reported one treatment-related AE each. A 9-year-old participant reported Grade 1 vomiting and a 10-year-old participant reported Grade 1 rash. Both the events were non-serious, occurred 2 days after study drug administration, and resolved without treatment for AE.

In the oseltamivir arm, 6 participants reported a total of eight treatment-related AEs. The events reported were vomiting (4 events in 4 participants), abdominal pain (1 event in 1 participant), and hypothermia (3 events in 1 participant). All eight AEs were Grade 1 in severity, non-serious, and resolved without treatment for AE.

Adverse Events by Intensity

All AEs were Grade 1 or 2 except for one Grade 4 AE and three Grade 3 AEs.

One participant (1.0%) experienced one Grade 4 AE (PT: agranulocytosis) and 3 participants (3.0%) experienced three Grade 3 AEs (PT: neutropenia, pneumonia mycoplasmal, and pneumonia). All the Grade 3 and 4 events were reported in the baloxavir marboxil arm. No severe AEs were reported in the oseltamivir arm.

The Grade 4 AE of agranulocytosis was reported in a 5-year-old participant with total neutrophil count of 0.49×10^9/L (normal range: 1.2−7×10^9/L). The Grade 3 AE of neutropenia was reported in a 2-year-old participant with total neutrophil count of 0.69×10^9/L (normal range: 1.2−7×10^9/L). Both events were identified on Study Day 6 from scheduled laboratory assessments. The investigator assessed both events as non-serious, not related to the study drug, and associated with the underlying disease. The two events resolved without medical intervention.

The other two Grade 3 AEs were cases of pneumonia mycoplasmal and pneumonia, both serious but considered unrelated to the study drug.

Adverse Events by Outcome

The majority of AEs were resolved (41/46 [89.1%] AEs in the baloxavir marboxil arm; 28/32 [87.5%] AEs in the oseltamivir arm) during the study.

One AE (PT: hyperuricaemia) in the oseltamivir arm had not resolved by the end of the study.

The outcome was unknown for 5 AEs (PT: monocytosis, blood creatine phosphokinase MB increased, blood triglycerides increased, C-reactive protein increased, and hyperphosphataemia) in the baloxavir marboxil arm and 3 AEs (PT: vomiting, blood lactate dehydrogenase increased, and blood triglycerides increased) in the oseltamivir arm.

Adverse Events by Timing of Onset

The incidence of AE by onset time was highest in both treatment arms between Days 1 and 7 and subsequently decreased between Days 8 and 14 and from Day 15 or later (Table 12). The onsets of the 2 SAEs in the baloxavir marboxil arm were within the Days 1−7 and Days 8−14; respectively. No observations of note with respect to the timing of AE onset were identified.

Table 12 Incidence of Adverse Events by Timing of Onset

	Baloxavir marboxil (N=66) n (%)	Oseltamivir (N=33) n (%)
Time of Onset		
Days 1-7	17 (25.8)	12 (36.4)
Days 8-14	3 (4.5)	0 (0)
Days 15 and later	8 (12.1)	4 (12.1)

N=number of participants.

Adverse Events by Dose of Baloxavir Marboxil

Of the 66 participants receiving baloxavir marboxil, 36 participants weighing<20 kg received body-weight adjusted dosing of 2 mg/kg and 30 participants weighing≥ 20 kg received a flat dose of 40 mg baloxavir marboxil. The overall incidence of AEs was numerically lower in the 2 mg/kg dose subgroup (30.6%)

compared with the 40 mg dose subgroup (43.3%), no meaningful differences in the nature and incidence of individual AEs were observed between the two dose subgroups (Table 13).

Table 13 Adverse Events by Dose of Baloxavir Marboxil Occurring in≥5% of Participants in Any Dose Subgroup

Preferred Term	2 mg/kg N=36 n (%)	40 mg N=30 n (%)
Participants with any AE	**11 (30.6%)**	**13 (43.3%)**
Diarrhoea	2 (5.6%)	1 (3.3%)
Vomiting	1 (2.8%)	2 (6.7%)
Bronchitis	3 (8.3%)	2 (6.7%)
Upper respiratory tract infection	1 (2.8%)	3 (10.0%)
Blood creatine phosphokinase MB increased	0	2 (6.7%)
Leukopenia	0	2 (6.7%)

AE=adverse event; N=number of participants.

Serious Adverse Events

Overall, 2 (3%) participants in the baloxavir marboxil arm experienced 2 SAEs (PT: pneumonia and pneumonia mycoplasmal; one participant each); both the events were Grade 3 and considered not related to the study drug by the investigator. No SAEs were reported in the oseltamivir arm.

The SAE of mycoplasma pneumonia was reported in a 10-year-old female participant, with onset on Day 4. Her initial influenza-related fever showed reduction by Day 3. On Day 4, the participant went shopping in the afternoon and subsequently developed a fever that evening. The SAE was treated with antibiotics and resolved after 11 days. The investigator evaluated this event as a community-acquired infection and not related to the study drug.

The SAE of pneumonia was reported in another 10-year-old female participant on Day 10. The diagnosis was accompanied by laboratory findings of an increased neutrophil count. The SAE was treated with antibiotics and resolved after 4 days. The investigator assessed this event as unrelated to the study drug, considering it a complication of influenza.

Adverse Events That Led to Discontinuation of Treatment or dose interruption

As baloxavir marboxil was a single-dose regimen, this was not applicable in the baloxavir marboxil arm. In the oseltamivir arm, no AEs led to discontinuation of treatment or dose interruption.

Pharmacokinetics

The PK analysis set comprised of 44 participants. Plasma samples were collected 0.5-2 hours, 24 hours, 72 hours and six days post-dosing. The baloxavir marboxil (pro-drug) plasma concentrations has been found to be below the limit of quantification for the vast majority of participants in previous studies. Therefore, in the current study, only the baloxavir plasma concentrations are measured and reported.

The mean baloxavir concentration-time curve following single dosing is shown in Figure 6. The mean baloxavir concentration-time curves stratified by body weight is shown in Figure 7.

Figure 6 - Plot of Mean Baloxavir (RO7248313) Concentrations over Time, Pharmacokinetic Analysis Set

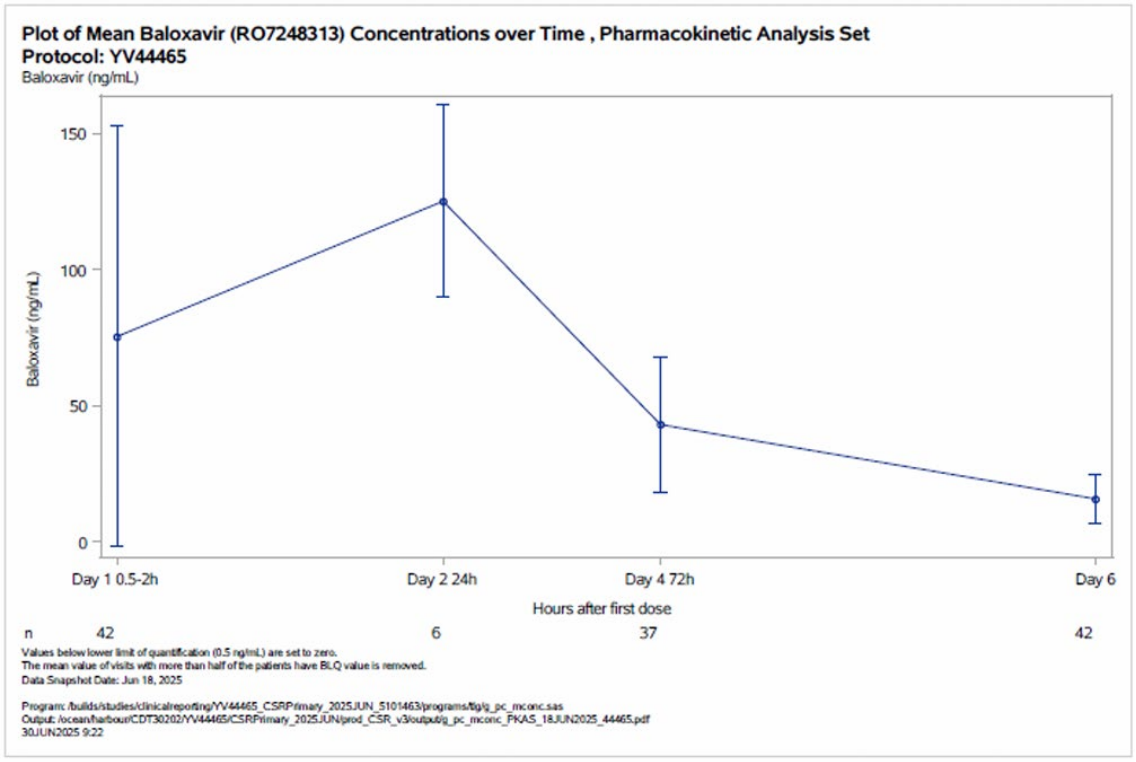
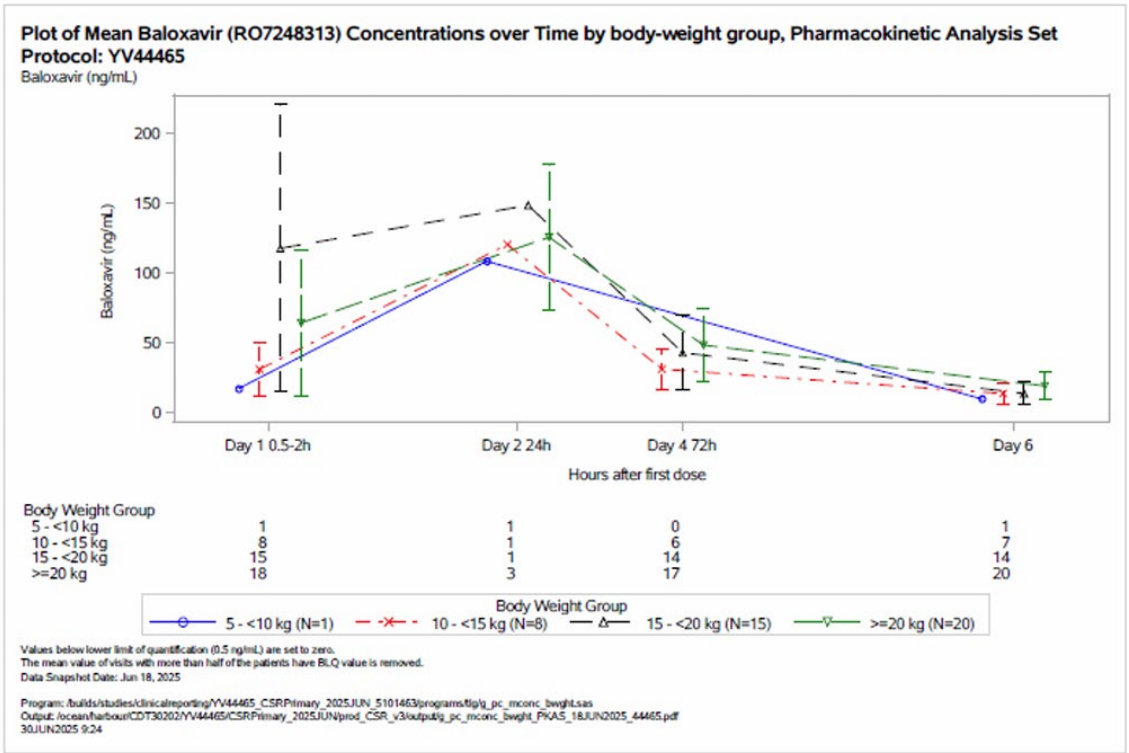


Figure 7 – Plot of Mean Baloxavir (RO7248313) Concentrations over Time by Body-Weight Group, Pharmacokinetic Analysis Set



The below Table 14 shows the concentration data at the different time points.

Table 14 - Summary of Baloxavir (RO7248313) Concentrations over Time, Pharmacokinetic Analysis Set

Summary of Baloxavir (RO7248313) Concentrations over Time, Pharmacokinetic Analysis Set
Protocol: YV44465

Analyte : RO7248313 by Baloxavir (ng/mL)

Visit Timepoint	Baloxavir Marboxil (N=44)
Visit 1 (Day 1)	
0.5 HR To 2 HR POSTDOSE	
n	42
Mean (SD)	75.49 (77.283)
CV % Mean	102.4
Median	49.70
Min - Max	0.0 - 394.0
Visit 2 (Day 2)	
24 HR POSTDOSE	
n	6
Mean (SD)	125.25 (35.225)
CV % Mean	28.1
Median	128.50
Min - Max	68.5 - 170.0
Visit 3 (Day 4)	
72 HR POSTDOSE	
n	37
Mean (SD)	43.15 (24.872)
CV % Mean	57.6
Median	39.00
Min - Max	6.9 - 101.0

Values below lower limit of quantification (0.5 ng/mL) are set to zero.
The mean value of visits with more than half of the patients have BLQ value is removed.
Data Snapshot Date: Jun 18, 2025

Summary of Baloxavir (RO7248313) Concentrations over Time, Pharmacokinetic Analysis Set
Protocol: YV44465

Analyte : RO7248313 by Baloxavir (ng/mL)

Visit Timepoint	Baloxavir Marboxil (N=44)
Visit 4 (Day 6)	
DAY 6	
n	42
Mean (SD)	15.86 (9.169)
CV % Mean	57.8
Median	12.20
Min - Max	3.8 - 34.2

Values below lower limit of quantification (0.5 ng/mL) are set to zero.
The mean value of visits with more than half of the patients have BLQ value is removed.
Data Snapshot Date: Jun 18, 2025

An independent population PK report for this study will be submitted separately, to assess and compare the population PK model derived parameters from this study with the Asian adult and adolescent population.

2.3.3. Discussion on clinical aspects

Pharmacokinetics: When comparing plasma levels of baloxavir,72-hours post-dosing with previous results, the concentrations are higher. From the SmPC section 5.2, the mean $C_{72\ hours}$ is between 10 and 19.1 ng/mL with a 95th percentile up to 39.2 ng/mL for non-Asian children between the age of 1 and 12 years old whereas the current study shows a mean $C_{72\ hours}$ of 43.15 ng/mL with a maximum of 101 ng/mL. The higher concentrations at 72 hours post-dose are not considered clinically meaningful as the safety profile is comparable and the applicant has stated that a PopPK report will be submitted later.

Overall, the efficacy results were comparable between the two treatment arms (including TTAS, duration of fever, duration of symptoms, time to return to normal health and activity, complications and the proportion of participants requiring antibiotics).

Subgroup analyses of time to alleviation of influenza signs and symptoms on the basis of age group showed a numerically faster alleviation in the baloxavir marboxil arm for 1-<5 years old group and comparable efficacy between the groups for 5-<12 years old.

Efficacy was also comparable between the groups for H1_2009 viral subtypes, the numbers of participants with other viral subtypes (H3 and B) were too low to interpret the data.

The overall incidence of AEs was similar between the baloxavir marboxil arm (24/66 [36.4%] participants) and the oseltamivir arm (12/33 [36.4%] participants). The most commonly reported AEs (≥5% of participants in either treatment arm; baloxavir marboxil arm vs. oseltamivir arm; respectively) were vomiting (4.5% vs. 18.2%), functional gastrointestinal disorder (3.0% vs. 6.1%), bronchitis (7.6% vs. 0%), upper respiratory tract infection (6.1% vs. 3.0%) and rhinitis (0 vs. 6.1%). The proportion of participants with AEs assessed as treatment-related by the investigator was numerically lower in the baloxavir marboxil arm than in the oseltamivir arm (2/66 [3.0%] participants vs. 6/33 [18.2%] participants; respectively).

The majority of AEs were Grade 1-2 in either treatment arm, with the exception of one Grade 4 AE (Preferred Term [PT]: agranulocytosis) and three Grade 3 AEs (PT: neutropenia, pneumonia mycoplasmal and pneumonia), all in the baloxavir marboxil arm which were all considered unrelated to the study drug by the investigator. Two participants in the baloxavir marboxil arm reported two SAEs (PT: pneumonia mycoplasmal and pneumonia; one participant each) which were both Grade 3 and deemed unrelated to the study drug. No SAEs were reported in the oseltamivir arm.

There were no deaths reported and no participant experienced an AE leading to withdrawal of study treatment or dose interruption and no adverse event of special interest (AESIs) reported during the study.

This study leads to no significant safety concerns and no new safety signals were identified for baloxavir marboxil. The safety profile of baloxavir marboxil in this population was generally consistent with the known safety profile of baloxavir marboxil.

No update of the Xofluza SmPC is warranted.

3. Rapporteur's overall conclusion and recommendation

☒ **Fulfilled:**

No regulatory action required.